SENTIREC

Sentinel Node Mapping with Robotic Assisted Near Infra-Red Fluorescent Imaging in Women with Cervical and Endometrial Cancer

- Project Description -

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Introduction

Lymph node metastasis is the most significant negative prognostic factor in women with cervical- and endometrial cancer. Surgical staging serves to allocate women with lymph node metastases to adjuvant therapy. For women with cervical cancer with tumours of >2 cm the standard surgical staging includes pelvic lymph node dissection (PLD) and additional paraaortic lymph node dissection (PALD) is recommended for women with high-risk histology endometrial cancer. PLD and PALD is associated with morbidity including blood loss, nerve injury, and lymphoedema.

Sentinel lymph node (SLN) mapping is a highly specialized surgical procedure, which may replace radical lymphadenectomy in many cancer diseases without compromising diagnostic safety. The technique has been described previously and has proved safe for detecting lymph node metastasis in early-stage cervical cancer (tumour < 2 cm) and in low-risk endometrial cancer, but has so far not been implemented in the daily clinical treatment of women with cervical and endometrial cancer in Denmark. The diagnostic safety of SLN mapping for identifying lymph node metastases in women with cervical cancer with tumours of >2cm and for women with endometrial cancer with high-risk histology is unclear. The risk of late effects e.g., leg and groin lymphoedema and its impact on quality of life after radical PLD and PALD has not been evaluated. In these studies, we will investigate if SLN mapping is a diagnostically safe staging modality for women with cervical cancer with tumours >2cm and for women with endometrial cancer with high-risk histology. Further, we will assess the patient experienced incidence of lymphedema and its impact on the quality of life after PLD and PALD.

Background

The systematic staging with PLD and PALD offers diagnostic information to allocate women to follow-up or adjuvant treatment. Two randomized controlled trials found no survival benefit of PLD (1,2). Lymph node involvement is observed in 12-22% of women with early-stage cervical cancer and in 20-30% with early-stage high-risk endometrial cancer (3–5). As a consequence, approximately 80% of the women undergoing PLD do not benefit from the procedure. There are several intra- and postoperative complications related to PLD including lymphedema, lymphocysts, neurovascular damage, ureteral injury, and blood loss (6–8). Following radical PLD, it is estimated that about 11-28% of women develop lower limb lymphedema that may give rise to heaviness, tingling, aching, numbness, and pain (9). These symptoms may be associated with decreased quality of life that is likely to impact on the woman's physical functioning and psychosocial- and sexual well-being (9–11).

Sentinel lymph node (SLN) mapping has proved diagnostically safe and is implemented in the treatment of breast, melanoma, and vulva cancer (12,13). The SLN mapping concept is based on two principles; lymphatic drainage follows an orderly and predictable pattern to a regional lymph node basin and the first lymph node in this pattern functions as an effective filter for tumour cells. Hence, the SLN is the first lymph node(s) to which the primary tumour metastasizes. If the sentinel node is without metastatic disease, theory is that all lymph nodes in that region are free of cancer

and complete lymph node removal is unnecessary (6,13). The technique has proved diagnostically safe in early stage cervical cancer (tumour < 2 cm) and in low-risk endometrial cancer (14).
The uterus is a midline structure with bilateral lymphatic drainage. The detection of SLNs per hemipelvis is therefore important to ensure complete removal of possible metastases (6). SLN mapping in cervical and endometrial cancer may have several advantages compared to radical PLD. The intra- and postoperative complications may decrease and the surgical procedure is shorter. Further, the SLN may be identified in areas (e.g. the paraaortic and presacral areas) that would have been ignored with standard PLD (15). In addition, the SLN technique allows the use of the ultra - staging technique that enables identifying micrometastases (16).

One of the main challenges of the SLN procedure is the rate of false negative procedures. However, studies in early stage cervical tumours have shown this rate to decrease significantly if SLN mapping is supplemented by removal of enlarged nodes, PLD in cases of failed SLN mapping, paraaortic evaluation, and ultra-staging (6,17) (Figure 1). Following this algorithm, one study showed a decrease in false negative procedures from 14.9% to 1.9% in women with endometrial cancer (17). Whether this algorithm will have equal safety in women with cervical cancer with tumours >2cm and women with high-risk endometrial cancer is unknown.

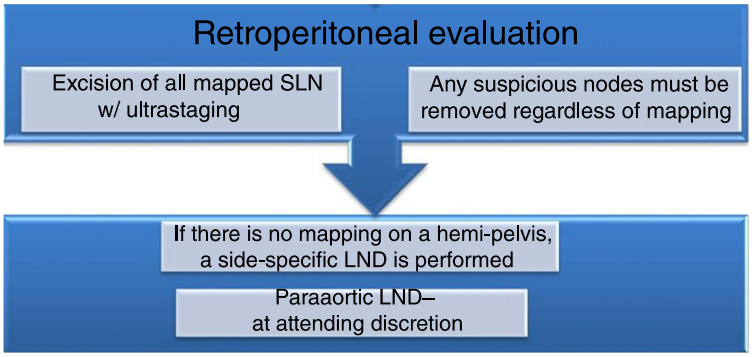

Figure 1: SLN algorithm for lowering the rate of false negative procedures (17).

The size of the primary cervical tumour has been suggested to influence on the diagnostic safety of SLN mapping. Hence, one study showed a significantly higher detection rate (94.0% vs. 83.6%) in tumours <=2 cm in size as opposed to larger tumours (18). However, additional studies are needed to further evaluate SLN mapping in cervical tumours > 2 cm.

For women with high-risk endometrial cancer most studies on the safety of SLN mapping has been based on mixed populations of high-risk and low-risk endometrial cancer patients (17,19,20). Despite this the only three false negative SLN cases in the SENTIENDO study, were found among high-risk patients. Further the sensitivity and NPV of SLN mapping in previous studies were calculated on women were the majority had PLD and not both PLD and PALD as a reference, with the risk of overseeing isolated para-aortic nodal metastasis (17,19,21). In the study by Barlin et al. the only false negative SLN case had an isolated paraaortic metastasis (17).

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is the most accurate imaging modality to detect lymph node- and peritoneal metastases in gynaecological

cancers (22). Previous studies have shown a comparatively high sensitivity and specificity of FDG-PET/CT to detect lymph node metastases in women with cervical cancer compared to other imaging modalities (23). For smaller cervical tumours and low volume metastasis several studies have shown a high false positive and false negative rate whereas FDG-PET/CT performed significantly better with higher tumour stage (22,23). In the group of women with cervical cancer and tumour size > 2 cm, FDG-PET/CT imaging may assist SLN mapping in detecting lymph node metastasis.

The accuracy of FDG-PET/CT is challenged for small-volume disease but may have a high sensitivity in detecting larger metastasis >10mm for both high-risk endometrial cancer and cervical cancers (24). By adding FDG-PET/CT to the SLN mapping the sensitivity for paraaortic macrometastasis might improve and thus minimising the risk of overseeing at least macroscopic paraaortic isolated metastasis. However, the role of FDG-PET/CT as an integrated part of an SLN algorithm for women with cervical cancer with tumours of >2cm and women with high-risk endometrial cancer and is still unsettled.

Even though SLN mapping with indocyanine green (ICG) shows a consistently high overall detection rate (78-100%) and a high bilateral detection rate (57-97%)in women with cervical cancer <2cm and low-risk endometrial cancer (3,18,25–28), the use of SLN mapping in larger cervical and endometrial cancer with high-risk histology is more doubtful. The present study will investigate if the combination of SLN mapping and a preoperative diagnostic FDG-PET/CT improves the detection of metastases in women with large cervical tumours (>2cm) and in women with high risk histology endometrial cancer.

Aims of the study

I. To evaluate the diagnostic safety of SLN mapping in combination with FDG-PET/CT imaging in women with cervical cancer with tumour size > 2 cm and in women with high-risk histology endometrial cancer
II. To evaluate the course of lymphedema in women with early-stage cervical (tumour>2 cm) following SLN mapping and PLD.
III. To evaluate the course of lymphedema following SLN mapping, PLD and PALD in women with high-risk endometrial cancer.

It is hypothesized that SLN mapping in combination with FDG-PET/CT imaging is a diagnostically safe technique in women with high risk cervical cancer (tumour >2cm) and in women with high-risk endometrial

It is further hypothesized that PLD- for cervical cancer and PLD+ PALD for high-risk endometrial cancer in combination with SLN mapping will lead to an incidence of chronic lymphedema (as measured 12 months postoperatively) of around 30%, leading to a significantly impaired quality of life.

Study population

- Study IIA: Women with cervical cancer (FIGO stage IB1, IB2 and IIA1) and a tumour size > 2 cm with planned robotic assisted laparoscopic radical surgery including radical hysterectomy and PLD are eligible.
- Study IIB: Women with presumed stage I high-risk endometrial cancer (Endometriorid adenocarcinoma grade 3 or Type 2 histology; serous adenocarcinoma, clearcell adenocarcinoma and carcinosarcoma) (32-33) planned for robotic assisted laparoscopic radical surgery including total hysterectomy, PLD and PALD are eligible.

Inclusion criteria:	- Women 18 years or older - Study IIA: patients with early stage cervical cancer with tumour size >2 cm*, FIGO stage IB1, IB2 or IIA1 - Study IIB: patients with high risk endometrial cancer, type 1 histology grade 3 Endometrioid adenocarcinoma or type 2 histology (serous-, clearcel-, carcinosarcoma or undifferentiated adenocarcinoma. - Capable of filling out questionnaire in Danish - Booked for robotic assisted operation
Exclusion criteria:	- Prior PLD - Known allergy towards ICG and/or iodine (ICG contains 5% sodium iodine) - Women included in other studies affecting outcome-measures of the present study - Women where pelvic lymphadenectomy is discarded or previously performed been deselected due to reasons related to the patients health status - Women in active treatment for a secondary cancer diagnosis within the past 5 years (excl. basal cell carcinoma) - Women with dementia

*The size of the cervical tumour will be determined by clinical evaluation in the diagnostic gynaecologic examination as customary.

Both studies will be commenced at Odense University Hospital. Copenhagen University Hospital from March 2017 and at Aarhus University Hospital from June 2018. International collaboration will be sought to assist in inclusion due to the low number of eligible patients in Denmark. Patients will be included over a three-year period from February 2017 to February 2020. A total of 100 patients in Study IIA and 150 patients in Study IIB (please see the power calculation) will be included in this two-year inclusion period. The study period may be extended until the expected number of patients are included

Study design

Both studies are prospective observational diagnostic studies with the purpose of investigating the diagnostic safety of SLN mapping and FDG-PET/CT to detect lymph node metastases. All patients will receive SLN mapping and removal of FDG-PET/CT positive lymph nodes followed by conventional radical PLD and for endometrial cancer also PALD.
Please see appendix 3-4 for flowcharts of the procedure.

FDG-PET/CT scans will be performed in all patients prior to surgery. An experienced specialist in nuclear medicine will systematically describe the FDG-PET/CT for each patient prior to surgery.

FDG-PET/CT positive lesions are described with exact anatomic localizations (appendix I), size and amount. All lesions will be evaluated on an ordinal scale ranging from 0 to 3. A score of 0 or 1 carry the meaning of 'no' or 'probably no' signs of metastasis, and a score of 2 or 3 carry the meaning of 'probable' or 'definite' signs of metastasis, respectively. For overall accuracy analyses, these values will be dichotomized into test negative (0 and 1) and test positive results (2 and 3). Furthermore, in all FDG avid lesions, the standard uptake value (SUV) will be registered for quantification purposes. Blood sugar levels will be taken on patients in order to calculate the SUV.

Surgical Procedure:

Shortly prior to surgery a vial of 25 mg ICG is diluted with 20 ml of sterile water to produce a 1.25 mg/ml concentration. For each patient, a new vial of ICG is used due to degradation of the fluorescence signal of ICG after dissolving. The same vial of ICG may however be used for several patients if the patients are operated the same day, since degradation of the fluorescence signal of ICG after dissolving is very low within the first 24 hours. When the woman has been anesthetized and immediately prior to surgery, 4 ml of the 1.25mg/ml ICG solution is injected into the cervix.. An injection of 2 ml will be made on each side of the cervix at positions 3 and 9 o'clock, with 1 ml deep in the cervical stroma (>10 mm) and 1 ml submucosally (< 5 mm).
The surgical robot is routinely docked and the NIR fluorescence system is initiated. All standard locations of a PLD are examined for fluorescence using the NIR fluorescence imaging system. Fluorescent hotspots are denominated as SLNs and the amount and localization are described and drawn into an anatomical illustration (Appendix I). All denominated SLNs are then removed surgically and sent for ultra-staging. The FDG-PET/CT positive lymph nodes will be localized following the SLN mapping. If the FDG-PET/CT positive lymph node has already been nominated as a SLN, the lymph node- will be labeled SLN and FDG-PET positive. Any enlarged lymph nodes suspicious of metastatic disease will be removed and marked as such with the predefined anatomical location (Appendix I). Finally radical PLD is performed in all women. Women with endometrial cancer will further undergo PALD to the level of the renal vein.

Pathology:

Removed SLNs are fixed in formalin after excision. A national ultra-staging protocol is implemented in all three participating centres. At the Department of Clinical Pathology the SLNs will be serially sectioned at 2-mm intervals in cross-section and entirely embedded in paraffin. The SLNs will be examined by the ultra-staging protocol consisting of four consecutive sections 5 µm thick, each obtained at 350 µm intervals according to the Danish guideline for SLN analysis in breast cancer. The first section at each level is stained with routine hematoxylin and eosin staining, the second section will be used for immunohistochemical staining for cytokeratin AE1/AE3 and the third section is available for additional analysis. Non SLNs will be examined conventionally through microscopy and routine hematoxylin and eosin staining of each block.
Histopathological features that will be recorded include tumor size, presence or absence of lymphovascular space invasion, the number of SLNs per case, the number of nonSLNs per case, the presence of metastases in SLNs and non-SLNs and the size and location of the metastasis in the SLNs.

Patients with histologically verified metastatic disease (including micro metastases) will be allocated to postoperative therapy according to national guidelines. Postoperative clinical follow up will be performed according to national guidelines.

Patient reported outcome measures

A combination of validated questionnaires are completed to assess the incidence of lymphedema and its impact on quality of life:

- Ten questions on lymphedema selected from the European Organization for Research and Treatment of Cancer (EORTC) Vulva Cancer Questionnaire Module (VU34) and included in the EORTC item bank: IL76. The questions will be used to screen for lymphedema, if the patient answers yes to any of the questions, they will be asked to complete the LYMPQOL questionnaire (please see below). Two items in the IL76 constitute a validated scale of leg lymphedema in women with cervical and endometrial cancer as entailed in the questionnaires EORTC CX24 and EN24.
- Lymphedema Quality of Life Questionnaire (LYMQOL) (29). A validated condition-specific quality of life assessment tool (Lymphedema Clinic, Derby Hospital NHS Foundation Trust, England).
- The generic questionnaire, EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (30) and the disease specific instruments for cervical (CX-24) and endometrial (EN-24) cancer

The LYMQOL questionnaire will be translated to Danish using independent forward-backward translation and pilot tested before administration.
The questionnaires are completed as paper/pen version or electronically at the patient's individual preference at 3, 12, 24, and 36 months after surgery. The incidence of early lymphedema will be evaluated at 3 months postoperatively as a difference score between 3 months and the baseline score. The course of chronic lymphedema will be evaluated over time. Written reminders will be sent once after three weeks at each questionnaire interval if the patient has not responded. Sociodemographic variables will be collected using a questionnaire designed for the purpose and included in the first questionnaire package. The sociodemographic variables include Danish social security number, age, hospital, date of inclusion, BMI, smoking status and contact information. Other data recorded from patient medical files include comorbidity, prior abdominal surgery, type of cancer, presumed preoperative FIGO stage, final FIGO stage postoperatively and whether or not the patient undergoes postoperative oncological therapy. This information will be used for stratification and adjustment in the analyses of lymphedema and quality of life.

Special considerations

In Study IIA radiologically and/or clinically suspected lymph nodes may be sent for frozen section to rule out the metastatic disease. Alternatively, a two-step procedure: removal of suspected lymph nodes for histology as a first step operation followed by completion surgery as a second step, if no metastatic disease in the removed lymph nodes is revealed. If metastatic lymph node involvement is histologically confirmed intra-operatively, the surgical procedure of women with cervical cancer will be terminated and the patient will be referred for chemo-radiotherapy.

In study IIB In case of clinically highly suspicious lymph nodes a frozen section evaluation is recommended, and if metastatic disease is identified, systematic PLD and PALD should be abandoned and replaced by removal of all clinically and by imaging suspicious lymph nodes in the pelvic and paraaortic area. All women with serous adenocarcinomas and with carcinosarcomas should further undergo infracolic omentectomy (31).

Primary outcome measurements

Study IIA: The overall sensitivity of SLN mapping combined with removal of FDG-PET/CT positive lymph nodes in the detection of lymph node metastases. Due to the low prevalence of the disease this study is primarily explorative.
Study IIB: The NPV of SLN mapping combined with FDG-PET/CT. Please see below for a power calculation.

Secondary outcome measurements

Study IIA:

- Prevalence of lymph node metastasis.
- The detection rate of SLNs. The positive- and negative predictive values of SLN mapping per patient and per hemi-pelvis.
- The positive- and negative predictive value, sensitivity and specificity analyses of FDG-PET/CT.
- The specific size of the cervical tumour determined by a combination of MR imaging, pathology and clinical evaluation will be described for comparison.
- Incidence and severity of lymphedema and quality of life assessment of all patients.

Study IIB:

- Prevalence of lymph node metastasis.
- The detection rate of SLNs in high risk endometrial cancer.
- The sensitivity of SLN mapping per patient.
- Incidence and severity of lymphedema and affection of quality of life after SLN mapping, PLD and PALD.
- Intra- and postoperative complications after surgery with SLN mapping, PLD and PALD.

Statistical analysis

Study IIA cervix cancer:

The exact prevalence of lymph node metastases in cervical cancers of > 2cm is not known from the literature. In studies including low risk cervical cancer patients (tumors < 20 mm) it has been estimated to be < 10%. The present study is explorative and will include 100 patients in Study IIA (cervical cancer) who have undergone PLD after SLN mapping.
Further, the rate of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) findings of PET/CT and SN mapping will be identified to assess the positive predictive value,

the negative predictive value, the sensitivity of PET/CT and SN mapping, respectively. Explorative comparisons will be made for each of the intervention tests (PET/CT and SN mapping).

Study IIB endometrial cancer:

Amendment 04.12.2020

The prevalence of lymph node metastasis in high-risk endometrial cancer has been reported to be around 18-25% in women with high- risk histology endometrial cancer. The known prevalence enables a power calculation for the negative predictive value (NPV). For a possible implementation of SLN mapping, an NPV of 94% is considered acceptable, and a confidence interval below 90% is deemed unacceptable for implementation of SLN mapping in clinical practice. The power calculation is based on women who undergo SLN mapping, followed by PLD and paraaortic lymph node dissection. Assuming the true incidence of metastasis is 20%, and the sensitivity of the SLN mapping algorithm is 96%, 150 women with PLD and PALD are needed to conclude that NPV is larger than 94% using a 95% one-sided exact Clopper–Pearson confidence interval.

Biological material

Lymph nodes in all studies will be removed as described and sent for analyses at the Department of Clinical Pathology. Biological material will not be stored in a biobank for further research in the present project. Biological material is stored in the Department of Clinical Pathology as customary with all histological specimens and may be retrieved for other purposes. This will demand a new ethical application and informed consent from the patients.

The lymph nodes will be fixed in formalin on the day of removal. Lymph nodes will be examined macroscopically and tissue will be excised for microscopy. The residual tissue will be stored for 4 weeks, in case there is a need for additional examination. On day 3 or 4 the tissue from the lymph nodes will be ready for HE and immunohistochemical examination. On day 5 or 6 results will be ready.

Microscopy glasses will be scanned and saved digitally in the pathology system. Only personnel in the Department of Clinical Pathology will have access to these images. The images will be saved for at least 5 years. Excised tissue will be saved as paraffin blocs eternally, as is standard with histological specimens in Denmark. The blocs will be safely locked away and patients can only be identified via the pathology system of which only personnel have access to.

Recruitment of patients

Patients will be recruited at their first visit to the outpatient clinic at the hospital during the diagnostic process and planning of treatment. The written patient information given to the patient during this visit. A doctor from the gynaecologic oncology team provides oral information on relevant study. The doctors work with treatment of patients with gynaecological cancer on a daily basis and are very competent in informing the patient thoroughly about the disease and treatment besides potential project participation. The doctor have sufficient time for the appointment and will not be disturbed by telephone calls in order to ensure that the conversation can proceed undisturbed. The participant will be made aware of the possibility of bringing a family member or other relation to the appointment besides the patient's right to have time to consider the information before entering the study.

If the patient requests further oral information, the patient will be asked if she is willing to be contacted by phone for further oral information by a doctor after a couple of days. Final consent to participate in the study is obtained in connection with one of the patient's visits to the hospital prior to surgery.
Patients are free to accept or decline participation and will receive a minimum of 24 hours to consider before entering the study. Each patient will have a contact person delegated and will receive contact information to this person in case of a need for further information about the study. Each patient must give informed consent before they can be included in the study and is free to withdraw consent at any time. Patients who withdraw consent will instead receive the best available conventional treatment according to the guidelines from the Danish Gynaecologic Cancer Group. Please see attachments regarding written and oral participant information for further information.

Publications

Positive as well as negative results and inconclusive results will be presented at relevant national and international scientific congresses and published in scientific journals. This project is expected to result in at least six publications related to two PhD studies on cervical cancer and endometrial cancer. Further, two-three publications are expected on each study. All patient information will be anonymous prior to publication.

Potential risks, side effects and complications

The risk of allergic reaction is 1 per 42000 (32). Approximately 30 minutes extra duration of surgery is estimated in patients who are allocated to receive SLN mapping followed by conventional PLD.

We expect no other side effects, risks or other disadvantages.

Ethical considerations

A potential advantage for the participants in the study is the possible detection of a SLN and thereby potential metastases in an area outside the standard area of PLD. Further, patients may benefit from the diagnosis of micro-metastases by the ultrastaging technique, both allowing correct allocation for adjuvant treatment and potential improvement in survival.

We believe that the results of the present study have advantages to the patients in the studies as well as to future patients with cervical and endometrial cancer. We believe that potential disadvantages outweigh the potential risks and complications related to the SLN mapping procedure. Intra- and postoperative complications will be closely monitored as part of the study.
We expect that the present project will have substantial significance in changing the national treatment strategy of early stage cervical and endometrial cancer patients. A significant part of these patients undergo a systematic radical surgical lymph node staging procedure (PLD +/- PALD) that has never shown any survival benefit and which is considered to carry a substantial risk of chronic lymphedema. For women with cervical tumours >2 cm and endometrial cancer with high-risk histology, the sentinel node technique has not been established as a diagnostically safe procedure. With the present study, we will assess the diagnostic safety of the SLN procedure in itself and in

combination with a systematic use of FDG-PET/CT. Establishing the evidence of diagnostic safety as described may save future patients from systematic lymph node dissection procedures and hence likely decrease the risk of early and chronic lymphedema.

Approvals

A permit for the use of ICG has been obtained and authorized for this project by the Danish Health Authority (Journal nr. 2015053824). Approval has been authorized from the Regional Committee on Health Research Ethics (Project-ID S-20150207 SRJ/csf) and the Danish Data Protection Agency (Journal nr. 15/52037). The study is in conformity with the principles of the Helsinki Declaration II. Patients will be under protection of the Danish Legislation of Treatment of Personal Data and the Danish Health Legislation.
Copenhagen University Hospital and Arhus University Hospital will participate with inclusion for study IIA and study IIB. A permit for the use of ICG has been obtained and authorized for this project for use at Copenhagen University Hospital and Aarhus University Hospital by the Danish Health Authority.

Quality assurance

Before inclusion in study IIA and study IIB all centres will go through the national SENTIREC pilot study to ensure a structured surgical training and surgeon proficiency in accurate SLN mapping at the participating cancer centres. All centres will performe at least 30 successful SLN mappings, with a total (uni- and bilateral) SLN detection of > 80%.

Before entering study IIA and IIB, all centres will be thoroughly introduced to the protocol at site visits. The protocol along with local instructions for procedures including written and video material will be introduced before the study start. Each centre will have a senior consultant as local responsible co-investigator for the project. Only named, experienced surgeons who perform robotic surgery and are allocated to the gynaecological oncological team at one of the centres will perform the surgical procedure in the study. Before and during inclusion national investigator meetings will be held annually to ensure change of experiences, procedure adherence, and continued proficiency.

Economy

Professor Ole Mogensen and Chief Physician, Ph.D. Pernille Tine Jensen at the Department of Gynaecology and Obstetrics at Odense University Hospital (OUH), Denmark have taken the initiative to begin this project in cooperation with Ph.D. student, MD Sara Elisabeth Sponholtz.
This PhD is work package two of the ROSOR project (Research On Surgical Robotics), a large multicentre project examining different aspects of robotic surgery in collaboration with The Maersk McKinney Moeller Institute, Denmark. The current project examines techniques in robotic surgery, while the other work packages will be examining robotic surgery from an economical point of view, general quality of life after robotic surgery, muscular skeletal influences on the surgeon and development of the robotic function.
The Ph.D. student Sara Elisabeth Sponholtz salary is financed by a one-year faculty scholarship of 500.000 DKK from The Faculty of Health Science, Southern University of Denmark (SDU). The second year's salary is financed by a 500.000 DKK grant from OUH's Ph.D. Fund (account number OL 10212036). The third year is financed by a 500.000 DKK grant from the ROSOR project (account

number OL 6109), which is financed through OUH's Frontliniepulje and The Danish Cancer Society. Extra salary expenses for year two and three are covered by Eva and Henry Fraenkels Fond (45.410 DKK) and Danish Cancer Research Fund (106.286 DKK). Sara Elizabeth Sponholtz is employed at the Clinical Institute, SDU, who will manage payment of salary. The Ph.D. student Sarah Marie Bjørnholts is employed at Aarhus University the faculty of health, her salary is fully financed by a PhD scholarship from Aarhus University.

All included centres cover expenses and running costs related to SLN mapping. At Odense University hospital external funding has been achieved for the ultrastaging procedures and the purchase of ICG tracer, the Danish Cancer Research Fund has partly funded Study IIB. At Aarhus University hospital external funding has been achieved for running costs in study IIB by the Vissing Fund. Patients will not receive compensation for participating in this project.

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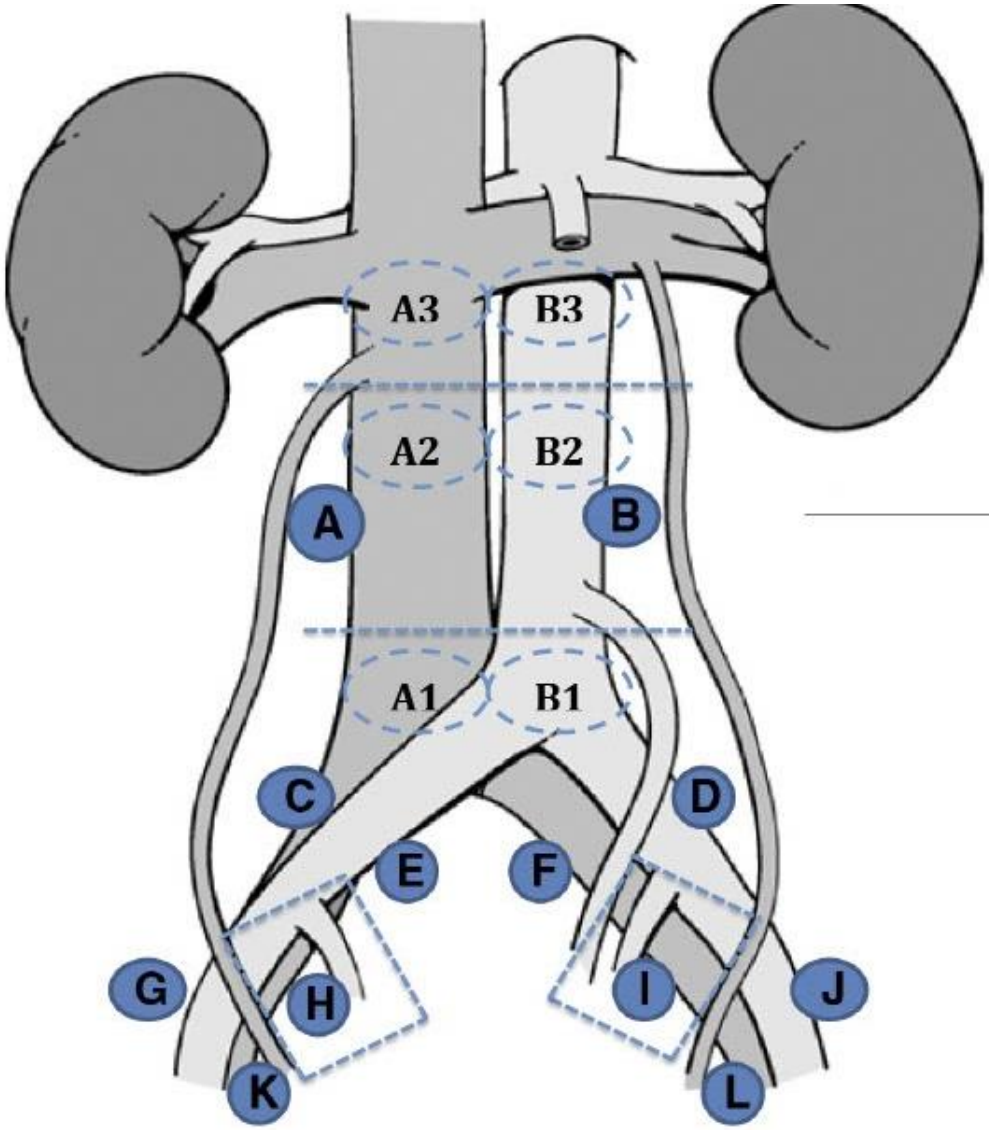
Appendix I. Predefined anatomical locations, for registration of lymph nodes.



Højre side:
A: Paraaortalt
A1= Under AMI
A2= Over AMI
A3= Ved højre nyrevene
C: Aa. Iliaca Communis
E: Præsakralt
G: A. Iliaca Externa
H: A. Iliaca Interna
K: Fossa Obturatoria

Venstre side:
B: Paraaortalt
B1= Under AMI
B2= Over AMI
B3= Ved venstre nyrevene
D: Aa. Iliaca Communis
F: Præsakralt
J: A. Iliaca Externa
I: A. Iliaca Interna
L: Fossa Obturatoria

1

Appendix II. English version of all included PROMS

EORTC IL76

ENGLISH

EORTC IL76

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
55.	Have you had swelling in one or both legs?	1	2	3	4
56.	Have you felt heaviness in one or both legs?	1	2	3	4
57.	Has the skin felt tight in your leg(s)?	1	2	3	4
58.	Have you had pain in your leg(s)?	1	2	3	4
59.	Have you had swelling in the genital area?	1	2	3	4
60.	Has the skin felt tight in your genital area?	1	2	3	4
61.	Have you had swelling in your groin?	1	2	3	4
62.	Have you had sore skin in your groin?	1	2	3	4
63.	Have you had pain in your groin?	1	2	3	4

LYMQOL LEG- *Scoring System*
Lymphoedema Quality of Life Tool

The score for the individual responses are given below. If the item is not scored and left blank or not applicable this is scored with a 0. Domain totals are calculated by adding the individual scores and dividing the total by the number of questions answered. (If >50% of questions per domain are not answered this cannot be calculated and =0).
The four domains and their corresponding questions are: Function 1 (a-f), 2,3 Appearance 4,5,6,7,8,9,10 Symptoms 11,12,13,14,15 and Emotion 16,17,18,19,20,21.
Overall quality of life (Q22) is scored as the value marked by the patient, between 0-10.

(Q1) How much does your swollen leg affect the following activities? **If any of the items are not applicable to you, please write N/A in the relevant answer box(es)**	**Not at all**	**A little**	**Quite a bit**	**A lot**
a) your walking	1	2	3	4
b) your ability to bend, e.g. to tie shoelaces or cut toenails	1	2	3	4
c) your ability to stand.	1	2	3	4
d) your ability to get up from a chair.	1	2	3	4
e) your occupation	1	2	3	4
f) your ability to do housework	1	2	3	4
(Q2)Does the swelling affect your leisure activities/ social life?	1	2	3	4

Please give examples of this .....

.....

(Q3) How much do you have to depend on other people?	1	2	3	4

	Not at all	**A little**	**Quite a bit**	**A lot**
(Q4) How much do you feel the swelling affects your appearance?	1	2	3	4
(Q5) How much difficulty do you have finding clothes to fit?	1	2	3	4
(Q6) How much difficulty do you have finding clothes you would like to wear?	1	2	3	4
(Q7) Do you have difficulty finding shoes to fit?	1	2	3	4
(Q8) Do you have difficulty finding socks/ tights/ stockings to fit?	1	2	3	4
(Q9) Does the swelling affect how you feel about yourself?	1	2	3	4
(Q10)Does it affect your relationships with other people?	1	2	3	4

LYMQOL LEG- scoring version May 2008

	Not at all	A little	Quite a bit	A lot
(Q11) Does your lymphoedema cause you pain?	1	2	3	4
(Q12) Do you have any numbness in your swollen leg(s)?	1	2	3	4
(Q13) Do you have any feelings of "pins & needles" or tingling in your swollen leg(s)	1	2	3	4
(Q14) Does (do) your swollen leg(s) feel weak?	1	2	3	4
(Q15) Does (do) your swollen leg(s) feel heavy?	1	2	3	4

In the past week….	Not at all	A little	Quite a bit	A lot
(Q16) Have you had trouble sleeping?	1	2	3	4
(Q17) Have you had difficulty concentrating on things, e.g. reading?	1	2	3	4
(Q18) Have you felt tense?	1	2	3	4
(Q19) Have you felt worried?	1	2	3	4
(Q20) Have you felt irritable?	1	2	3	4
(Q21) Have you felt depressed?	1	2	3	4

(Q22) Overall, how would you rate your quality of life at present?
Please mark your score on the following scale:

0 1 2 3 4 5 6 7 8 9 10
poor **excellent**

Thank you for completing this form.
If you have any comments or queries about it, please discuss these with ……..

Dr V L Keeley, Consultant

Questions 16 to 21 have been reproduced with permission from the EORTC.
These questions are only a part of the QLQ-C30 Questionnaire.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had cramps in your abdomen?	1	2	3	4
32. Have you had difficulty in controlling your bowels?	1	2	3	4
33. Have you had blood in your stools (motions)?	1	2	3	4
34. Did you pass water/urine frequently?	1	2	3	4
35. Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36. Have you had leaking of urine?	1	2	3	4
37. Have you had difficulty emptying your bladder?	1	2	3	4
38. Have you had swelling in one or both legs?	1	2	3	4
39. Have you had pain in your lower back?	1	2	3	4
40. Have you had tingling or numbness in your hands or feet?	1	2	3	4
41. Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42. Have you had discharge from your vagina?	1	2	3	4
43. Have you had abnormal bleeding from your vagina?	1	2	3	4
44. Have you had hot flushes and/or sweats?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47. Have you felt dissatisfied with your body?	1	2	3	4

Please go on to the next page

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:	Not at all	A little	Quite a bit	Very much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

ENGLISH

EORTC QLQ – EN24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had swelling in one or both legs?	1	2	3	4
32. Have you felt heaviness in one or both legs?	1	2	3	4
33. Have you had pain in your lower back and / or pelvis?	1	2	3	4
34. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
35. Have you passed urine frequently?	1	2	3	4
36. Have you had leaking of urine?	1	2	3	4
37. Have you had pain or a burning feeling when passing urine?	1	2	3	4
38. When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
39. Have you had any leakage of stools?	1	2	3	4
40. Have you been troubled by passing wind?	1	2	3	4
41. Have you had cramps in your abdomen?	1	2	3	4
42. Have you had a bloated feeling in your abdomen?	1	2	3	4
43. Have you had tingling or numbness in your hands or feet?	1	2	3	4
44. Have you had aches or pains in your muscles or joints?	1	2	3	4
45. Have you lost hair?	1	2	3	4
46. Has food and drink tasted differently from usual?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you felt less feminine as a result of your disease or treatment?	1	2	3	4

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
49. To what extent were you interested in sex?	1	2	3	4
50. To what extent were you sexually active?	1	2	3	4
Answer these questions only if you have been sexually active during the past 4 weeks:				
51. Has your vagina felt dry during sexual activity?	1	2	3	4
52. Has your vagina felt short and / or tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4